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Vitamin D Endocrine System and Psoriasis Vulgaris – Review of the Literature

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SUMMARY Vitamin D exerts its physiological functions on calcium and bone metabolism in humans through the active metabolite 1,25-dihydroxyvitamin D3(1,25(OH)2D3). The other spectrum of vitamin D activities includes important effects on cellular proliferation, differentiation and the immune system. These effects are mediated through the intracellularly located vitamin D receptor (VDR). VDR is a member of the steroid, estrogen and retinoid receptor gene family of proteins that mediate transcriptional activities of the respective ligands. The VDR complex binds in the nucleus to the vitamin D responsive element on the gene. Several polymorphisms of the vitamin D receptor (VDR) gene have been described including *Fok*I in exon 2, *Bsm*I and *Apa*I in intron 8 and *Taq*I in exon 9. Alterations in vitamin D-1,25 (OH)2D3 levels and polymorphisms of VDR gene have been shown to be associated with several malignant or autoimmune diseases such as sclerosis multiplex, breast cancer, diabetes mellitus, malignant melanoma, and psoriasis vulgaris. The effects of VDR gene polymorphisms including immunomodulation, stimulation of cellular differentiation and inhibition of proliferation make it a possible candidate for therapy of psoriasis as well as for the psoriasis gene modification. The objective of this article is to present the state-of-the-art in the VDR gene polymorphism research in psoriasis vulgaris.

KEY WORDS: vitamin D receptor gene, polymorphisms, psoriasis

The vitamin D endocrine system is central to the control of bone and calcium homeostasis. However, vitamin D has also been shown to play an important role in other metabolic pathways such as immune response and cancer (1).

VITAMIN D METABOLISM

Vitamin D3 is a fat-soluble prehormone, which plays an important role in many biologic functions throughout the body. Two thirds of the vitamin D3 content of the human body are synthesized from the precursor molecule 7-dehydrocholesterol in

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the skin by the action of sunlight, and one third is obtained from diet (2).

After UVB exposure, vitamin D3 enters blood circulation and binds to the vitamin D binding protein (DBP) (3), which carries vitamin D3 to the liver and kidney (4) for bioactivation. In the first activation step, vitamin D3 is hydroxylated by the enzyme 25-hydroxylase to 25-hydroxyvitamin D3 (25OHD3), mainly in the liver. In the second step, the biologically active hormone 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) is generated by hydroxylation of 25OHD3. This reaction is catalyzed by the enzyme 25-hydroxyvitamin D3-1-α-hydroxylase (1-α-hydroxylase) and it occurs mainly in the kidney (5). The active hormone stays in blood circulation for about 7 hours. As a fat soluble molecule, 1,25(OH)2D3 penetrates easily the plasma membrane of its target cells, where it is catabolized (6).

ACTIONS OF VITAMIN D

The 1,25(OH)2D3 regulates several functions in the body by modulating genomic events *via* its nuclear receptor. Classically, the main role of 1,25(OH)2D3 is regulation of serum calcium and phosphorus concentrations *via* actions in bone, parathyroid gland, kidney and intestine, which are considered as classic target organs for 1,25(OH)2D3. In addition, 1,25(OH)2D3 is able to generate several other biologic responses (non-classic actions of vitamin D) that are not related to the control of mineral homeostasis. Today, there are over 30 non-classic target tissues for 1,25(OH)2D3 (7).

In addition to the genomic actions, 1,25(OH)2D3 is also able to generate rapid biologic responses, which do not require any protein synthesis as genomic actions do (8). There is also evidence that rapid responses are able to modulate the genomic pathway of 1,25(OH)2D3 actions *via* phosphorylation of nuclear vitamin D receptor (VDR). Receptor phosphorylation could increase the affinity of VDR to coactivator complexes and thus enhance gene activation (9).

Immunomodulatory effects

Vitamin D3 is an important immunomodulatory hormone that activates monocytes, stimulates cell-mediated immunity, influences cytokine synthesis and suppresses lymphocyte proliferation (10). VDR and 1,25(OH)2D3 play a role in the Th1/Th2 balance through transcriptional inhibition of cytokine genes that are either required for Th1 differentiation or are products of differentiated Th1 cells. Active 1,25(OH)2D3 has been found to inhibit Th1 cytokines interferon gamma (IFN-γ) and interleukin-2 (IL-2), suppressing the production of pro-Th1 cytokine IL-12 by antigen presenting cells. 1,25(OH)2D3 has also been reported to increase Th2 cytokine IL-4 (11). In dendritic cells, calcitriol suppresses the expression of major histocompatibility complex (MHC) class II molecules and co-stimulatory molecules including CD40, CD80 and CD86, stimulates the production of IL-10 and inhibits the production of IL-12, leading to the suppression of T cell activation (12).

VITAMIN D RECEPTOR

The genomic actions of 1,25(OH)2D3 are mediated by its nuclear receptor, whose cDNA was first cloned from chicken in 1987 and shortly thereafter from human (13). VDR protein is a nuclear hormone receptor (NHR), a member of the steroid, estrogen, and retinoid receptor gene family of proteins, mediating the action of 1,25(OH)2D3 by controlling the expression of hormone sensitive genes (14). The VDR complex binds in the nucleus to the vitamin D responsive element in regulatory regions of target genes and changes the gene transcription (15). It is found on the cells of many different tissues, including the thyroid, bone, kidney and T cells of the immune system (16).

In humans, VDR protein consists of 427 amino acids, with a molecular mass of ~48 kDa. Like other NHRs, VDR can be divided by function into several domains. At the amino terminus there is an A/B domain 20 amino acids long. The DNA-binding domain (DBD), also termed C domain, locates between amino acids 21 and 92. The D or flexible linker region locates approximately between amino acids 93 and 123, followed by the E or ligand binding domain (LBD) between amino acids 124 and 427 (Fig. 1) (15).

Skin cells (keratinocytes, fibroblasts and other cells) express VDR. The presence of this receptor has been examined in human skin and in cultures

Figure 1. Schematic presentation of vitamin D receptor domain structure (A/B domain; DBD or DNA, binding domain; D or flexible linker region; E or ligand binding domain, LBD).

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of human epidermal keratinocytes and human dermal fibroblasts (17). Immunohistochemical studies of normal skin have shown VDR antigens to be expressed in keratinocytes of all epidermal layers (except those of the stratum corneum) and in cells of epidermal appendages. Some 50%-65% of Langerhans' cells, monocytes, and T-lymphocytes in the normal skin express VDR (18).

VDR gene

The human vitamin D receptor gene (h*VDR*) is a product of the single chromosomal gene, which is found on chromosome 12, localized to 12q13.11, and spans 75 kb, covering 62 359 base pairs (bp). The h*VDR* consists of eleven exons, of which the 5' non-coding region contains three exons (1A, 1B, and 1C) and the remaining eight exons (exons 2-9) encode the structural portion of the VDR gene product. Promoters for the h*VDR* are found in exons IF, IA and ID. They do not contain a TATA-box, although they are GC rich. This region causes differential splicing of transcripts. Three VDR mRNA transcripts are synthesized depending on how exons 1A, 1B, and 1C are spliced to form a mature mRNA transcript from which VDR protein can be translated (1,19).

VDR polymorphisms

Polymorphism is a genetic variant that appears in at least 1% of the population. These changes can occur in non-coding parts of the gene (introns), and they would not be seen in the protein product. However, changes in the exonic parts of the DNA lead to changes in protein sequence.

More than 25 polymorphisms are currently known for the *VDR* locus. These occur mostly near the 3' end but also towards the 5' end, in and near the promoter region (Fig. 2). More than 10 known polymorphisms exist in the 3' UTR including a poly(A) repeat polymorphism. Other single nucleotide polymorphisms (SNPs) in the *VDR* include the G to A polymorphism in the binding element of *Cdx*-2 (exon IE) as well as the functional *Fok*I polymorphism in exon II. The SNPs *Bsm*I and *Apa*I in intron VIII, *Taq*I in exon IX and the poly(A) repeat polymorphism in the 3' UTR within exon IX is located in an island of linkage disequilibrium (LD) forming haplotype alleles (20).

The *Cdx*-2 polymorphism in the promoter region of the h*VDR* gene lies close to the SNP found in the center of exon II (*Fok*I). *Cdx*-2 plays a crucial role in intestine-specific *VDR* gene expression, as it is able to activate *VDR* gene transcription. (21).

The *Fok*I polymorphism (alleles F/f corresponding to nucleotides C/T) is found in this exon and increases the overall length of the *VDR* transcript by 9 bp. While the *Fok*I polymorphism is the most credible candidate for a functional change, *Fok*I might be a marker for a nearby functional polymorphism within the *VDR* or nearby gene (22).

The 3'-end of the gene is particularly rich in polymorphisms. The *Tru*9I (TR/tr corresponding to nucleotides G/A) (23), *Bsm*I (B/b corresponding to nucleotides G/A) (24), and *Apa*I (A/a corresponding to nucleotides T/G) (25) polymorphisms are located in intron VIII, and are in strong LD with each other and with the silent *Taq*I polymorphism (T/t corresponding to nucleotides T/C) found in exon IX (26). Although the *Bsm*I and *Apa*I loci are intronic, a number of mechanisms have been invoked to explain how these polymorphisms might influence the expression of VDR. One of these explanations includes disruption of the splice site for *VDR* mRNA transcription, which may result in truncated or alternatively spliced protein products. Another explanation involves changes in mRNA stability speculating that these introns might influence the level of mRNA product (27).

More than 10 different sequence variants in the 3'-end untranslated region (UTR) have been described, including the poly(A) repeat polymorphism (27). The poly(A) polymorphism consists of variations in the number of the adenosine residues repeated. Ingles *et al*. (28) broadly divided a stretch of 17 poly-A's as the short (S) allele and ≥18 poly-A's as the long (L) allele. This L/S polymorphism is in LD with the *Bsm*I, *Apa*I and *Taq*I polymorphisms in intron VIII and exon IX, although LD differs between populations. The *Taq*I polymorphism results in a silent mutation in exon 9,

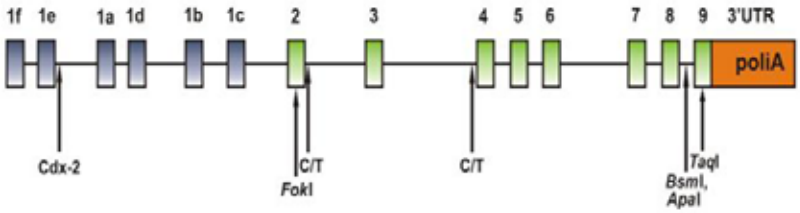

Figure 2. Vitamin D receptor polymorphisms.

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with ATT and ATC both coding for isoleucine. LD between *Bsm*I, *Apa*I and *Taq*I has led to various haplotype studies involving these polymorphisms (29).

VDR gene polymorphisms and psoriasis vulgaris

Psoriasis is a common, chronic inflammatory and hyperproliferative skin disease. Clinical lesions are results of hyperproliferation and abnormal differentiation of keratinocytes and epidermis infiltration with inflammatory cells including T cells and neutrophils. The etiology of psoriasis involves genetic, immune and environmental factors. In addition to the association with HLA gene on chromosome 6q21, other genes are also included in the disease onset (30). Previous studies on psoriasis and VDR gene have demonstrated both non-significant and significant associations, however, with different polymorphisms involved (31-39).

In addition to the classic action on calcium homeostasis and bone metabolism, calcipotriol inhibits proliferation and induces terminal differentiation of keratinocytes. It has been reported that cultured fibroblasts and keratinocytes from psoriatic patients exhibit partial resistance to calcipotriol mediated anti-proliferative activity, and response to calcipotriol treatment has been shown to vary among these patients (40).

VDR gene polymorphisms may explain this variable responsiveness. There have been a number of studies to investigate whether VDR gene polymorphisms could be a risk factor for the development of psoriasis in different populations.

It is known that VDR genotype distribution varies dramatically due to ethnic composition and genetic background of the population, and sample size (31). Some studies have reported a correlation between individual VDR genotypes (*Bsm*I, *Taq*I, *Apa*I or *Fok*I) and skin eruptions or efficacy of treatment with vitamin D analog (35).

Park *et al*. have reported a significantly higher frequency of the A allele by *Apa*I in psoriatics than in healthy controls, and the tendency was more accentuated in early-onset psoriasis. They also report a significant association between VDR genotype and mean age at onset. The authors suggest that VDR gene might be one the candidate genes implicated in the pathogenesis of psoriasis in the Korean population (31).

Okita *et al*. studied allelic frequencies of VDR in 86 normal subjects and 50 psoriatics. All subjects enrolled in this study were Japanese. The frequencies of *Apa*I, *Bsm*I and *Taq*I genotypes in psoriatics showed no significant differences compared with control subjects. The distribution of *Apa*I, *Bsm*I and *Taq*I VDR genotypes showed no significant relationship to the PASI score or age at onset (32).

In another study from Japan, the frequency of TT genotype was found to be higher in patients than in control (87% *vs*. 74%; $P<0.05$). They also showed that B allele and t allele were lower in patients than in controls. They found the VDR gene polymorphisms to be associated with psoriasis in Japanese patients (33).

Two related studies were conducted in Turkey. Kaya *et al*. investigated the association between VDR gene polymorphisms and psoriasis in Turkish patients. They demonstrated an association between aa/AA genotypes and 53 psoriasis patients compared to 54 healthy controls (AA: 26.4% *vs*. 50%; Aa: 58.5% *vs*. 38.9%; and aa: 15.1% *vs*. 11%) (34).

In contrast, Dayangac-Erden *et al*. showed that there was no significant difference in *Apa*I polymorphisms between Turkish patients and controls (AA: 23.5% *vs*. 30%; Aa: 56.9% *vs*. 55%; aa: 19.6% *vs*. 15%; $P\leq1$). However, in the study population consisting of 51 Turkish familial psoriasis patients (psoriasis vulgaris and psoriatic arthritis) and 100 healthy subjects, the frequency of TT genotype was found to be significantly higher in patients than in controls (73.5% *vs*. 59.5%; $P\leq0.025$). In psoriatic arthritis patients, the frequency of T allele was even higher (91.7%; $P\leq0.05$). The authors conclude that VDR gene *Taq*I polymorphisms are associated with familial psoriasis in the Turkish population. The authors explain the discrepancy of these results by the heterogeneous genetic composition of their study subjects examined at Hacettepe University in central Turkey (35).

In the latest related study in Europe, performed by Ruggiero *et al*., found the VDR gene polymorphisms not to be associated with psoriasis in the Italian Caucasian population (39). The role of VDR polymorphism analysis in predicting clinical response to calcipotriol was investigated in only a few studies, with controversial results (33,36-38).

In conclusion, the discrepancy of results reported from studies on VDR gene polymorphisms (onset or therapy of disease) might be explained by 1) genetically different populations; 2) size of the population samples; and 3) therapeutic response to different therapeutic agents administered in different concentrations. It should be noted that most

of these studies included small numbers of subjects, which could be the main reason for conflicting results.

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